Date: 17 June 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Evrysdi

International non-proprietary name: Risdiplam
Pharmaceutical form: powder for oral solution
Dosage strength: 0.75 mg/ml
Route(s) of administration: oral
Marketing Authorisation Holder: Roche Pharma (Schweiz) AG
Marketing Authorisation No.: 67251
Decision and Decision date: approved on 06 May 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ASO	Antisense oligonucleotide
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
BSID-III	Bayley Scales of Infant and Toddler Development – Third Edition BW body weight
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	Compound muscle action potential
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GLP	Good Laboratory Practice
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE-2	Hammersmith Infant Neurological Examination Module 2
HPLC	High Performance Liquid Chromatography
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
IV	Intravenous
LoQ	List of Questions
M1	Inactive main metabolite of risdiplam
MAH	Marketing Authorisation Holder
MATE	Multidrug and toxin extrusion
Max	Maximum
MFM32	Motor function measure 32
MID	Midazolam
Min	Minimum
mRNA	Messenger ribonucleic acid
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PD	Pharmacodynamics
Pgp	P-glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
Rh	relative humidity
RIS	Risdiplam
RMP	Risk Management Plan
RULM	Revised Upper Limb Module
SMA	Spinal muscular atrophy
SMAIS	SMA Independence Scale

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

SMDs	standardised mean differences
SMN	Survival motor neuron
SMN1	Survival motor neuron 1 gene
SMN2	Survival motor neuron 2 gene
SwissPAR	Swiss Public Assessment Report
$T_{1/2}$	Half-life
Tmax	Time to reach Cmax
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
Vz/F	Apparent central volume of distribution during terminal phase

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance risdiplam of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 15 October 2018.

2.2 Indication and Dosage

2.2.1 Requested Indication

Therapeutic indications
Treatment of spinal muscular atrophy (SMA).

2.2.2 Approved Indication

Evrysdi is indicated for the treatment of 5q-associated spinal muscular atrophy (SMA) in patients 2 months of age and older.

2.2.3 Requested Dosage

Evrysdi is taken orally once a day using the reusable oral syringe provided, at approximately the same time each day.
The recommended once daily dose of Evrysdi for SMA patients is determined by age and body weight (see table 1)

Table 1. Dosing regimen by age and body weight

Age and body weight	*Recommended Daily Dose*
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

Dosage changes must be made under the supervision of a healthcare professional. Treatment with a daily dose above 5 mg has not been studied. No data are available in infants below 2 months of age.

2.2.4 Approved Dosage

(see appendix)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2.3 Regulatory History (Milestones)

Application	19 August 2020
Formal control completed	20 August 2020
List of Questions (LoQ)	22 October 2020
Answers to LoQ	26 January 2021
Predecision	17 March 2021
Answers to Predecision	13 April 2021
Labelling corrections	29 April 2021
Answers to Labelling corrections:	3 May 2021
Final Decision	6 May 2021
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical Context

Spinal muscular atrophy (SMA) is an autosomal recessive disease with survival motor neuron (SMN) protein deficiency that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. Type 1 infantile-onset SMA is fatal, usually by 2 years of age, due to respiratory failure and infection.

There are multiple types of SMA (0-4), as shown in the following listing. Classification into SMA types has historically been based on the age of symptom onset and the maximal achieved motor abilities. In general, the severity of symptoms decreases and the age of onset is delayed with increasing survival motor neuron 2 gene (SMN2) copy number and correspondingly increasing amounts of SMN protein, although different patients with the same SMN2 copy number can have different clinical phenotypes.

Classification of spinal muscular atrophy

Type	**Age of onset**	**Maximum function achieved**	**Prognosis**	**Proposed subclassification**	**SMN copy number**
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	-	-
Type 1 (severe)	0–6 months	Never sits	If untreated, life expectancy<2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period	One or two copies of SMN2 in 80% of patients
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2.1 to 2.9	Three copies of SMN2 in>80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset of weakness before 3 years; 3B, onset of weakness after 3 years	Three or four copies of SMN2 in 96% of patients
Type 4 (adult)	10–30 years	Stands and walks	Survival into adulthood	-	Four or more copies of SMN2

Source: according to *Mercuri et al. 2012, Lancet Neurol 2012; 11: 443–52*

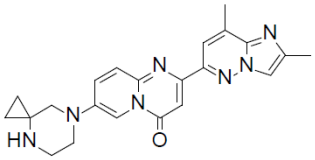
Approved treatments for SMA in Switzerland (April 2021):
The only currently approved treatment for SMA in Switzerland is Spinraza® (nusinersen). According to the publicly available information (for details see www.swissmedicinfo.ch), Spinraza is an antisense oligonucleotide (ASO) for intrathecal injection, indicated for the treatment of 5q-associated spinal muscular atrophy (SMA).

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Quality Aspects

4.1 Drug Substance

INN: Risdiplam
Chemical name: 7-(4,7-Diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)-*4H*-pyrido-[1,2-*a*]pyrimidin-4-one
Molecular formula: $C_{22}H_{23}N_7O$
Molecular mass: 401.46 g/mol
Molecular structure:



Physico-chemical properties:
Risdiplam is a light yellow or yellow or greyish yellow or greenish yellow powder with an achiral structure. The compound is practically insoluble in water and is non-hygroscopic. Risdiplam exhibits polymorphism. The commercial manufacturing process delivers the anhydrous Form-A.

Synthesis:
The synthesis of risdiplam consists of several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials, critical steps and intermediates.

Specification:
The drug substance specification includes tests for description (appearance and colour), identity, assay, organic impurities, water content, residual solvents, residue on ignition, elemental impurities and particle size distribution. The applied limits are justified and in line with the relevant guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability:
The stability of the drug substance was investigated with commercial scale batches manufactured by the proposed commercial manufacturing site. The stability samples were stored under long-term conditions (30°C/75% rh) and accelerated conditions (40°C/75% rh) as defined in the corresponding ICH Guideline on stability studies. Based on these studies, an adequate retest period was defined.

4.2 Drug Product

Description and composition:
Evrysdi powder for oral solution 0.75 mg/mL is a powder for constitution. Each bottle filled with 2.0 g of powder contains 60 mg of risdiplam (free base). The powder must be constituted with purified water to yield 80 mL of clear oral solution with a concentration of 0.75 mg/mL. The powder contains well known excipients.

Pharmaceutical development:
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including principles of quality by design as described in ICH Guidelines Q8 to Q11.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Manufacture:
Evrysdi powder for oral solution is manufactured by a standard granulation process. Control of the manufacturing process is ensured through defined operating parameters based on results of the development studies. In addition, in-process controls with adequate acceptance criteria are established.

Specification:
The drug product specifications include tests for description of bottle content, reconstituted solution (appearance, colour, pH), identification of risdiplam, identification of sodium benzoate, identification of ascorbic acid, content per bottle of risdiplam, content per bottle of sodium benzoate, content per bottle of ascorbic acid, degradation products by HPLC, uniformity of dosage units, water content, uniformity of mass of delivered doses and microbial limits. The proposed acceptance criteria and analytical methods were considered appropriate for quality control of the drug product.

Container Closure System:
Evrysdi powder for oral solution is packaged in glass bottles.

Stability:
Appropriate stability data from commercial scale batches of Evrysdi powder for oral solution are provided. The stability study was carried out according to ICH stability guidelines. Based on the results of this study, an adequate shelf life was established.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Nonclinical Aspects

The applicant submitted a comprehensive nonclinical study package to support the marketing authorisation application for Evrysdi. Pivotal toxicology studies were conducted in compliance with GLP. In addition to the submitted studies, the Swissmedic Division of Nonclinical Assessment also considered the approved FDA label for Evrysdi.

Pharmacology

Risdiplam dose-dependently increased the survival of motor neuron (SMN) protein levels in fibroblasts and motoneurons derived from human spinal muscular atrophy (SMA) patients by correcting the dysfunctional splicing of the human *SMN2* gene. In two genetic mouse models of SMA, alternative splicing of *SMN2* gene by risdiplam led to the generation of full-length SMN2 mRNA and to the production of the functional SMN protein.

Intraperitoneal and oral administration of risdiplam (0.3 to 3 mg/kg/day) in two SMA mouse models led to a dose-dependent increase of SMN protein in plasma, brain and muscles with no sign of toxicity. Risdiplam specificity for *SMN2* vs. *SMN1* gene was shown by the lack of splicing modifying effect on *SMN1* gene. Risdiplam treatment also induced a prolongation of animal survival and motor function in a mouse model of SMA, in addition to a dose-dependent normalisation of weight gain and reduced muscle atrophy.

The metabolite M1 exhibited a negligible primary pharmacological effect when compared to risdiplam. *In vitro*, risdiplam and M1 (10 µM) inhibited cyclooxygenase I and 2 (COX1 and COX2) activities by >84% and acetylcholinesterase by >77% and inhibited binding at histamine H3 (78%) and muscarinic M1 (54%) receptors. Given the total C_{max} of 93.2 ng/mL (i.e. 0.232 µM) in humans, clinically relevant off-target interactions are considered unlikely. Safety pharmacology studies did not show any evidence of effects of risdiplam on cardiovascular, central nervous system or respiratory functions.

Pharmacokinetics

Pharmacokinetic properties of risdiplam were studied in cynomolgus monkeys, rats, rabbits as well as in wild-type or genetically modified SMA mouse models. Risdiplam showed a short half-life in monkeys (~4 h) after both single IV and oral administration and a moderate oral bioavailability of 42.6%. After repeat-dose oral administration, the exposure increased roughly dose proportionally in all tested species. Orally treated rat pups exhibited a longer $t_{1/2}$ and residence time than adult rats. The mean free fraction of risdiplam in human plasma was 11%. Albumin was the main plasma binding protein for risdiplam. Plasma protein binding in adults was comparable in all species. In rats, monkeys, and humans, risdiplam was the primary drug-related component in plasma. It penetrated readily into brain in young and adult mice with similar C_{max} and T_{max} in plasma and brain tissue. Risdiplam was the major circulating component in rats following oral or IV administration. Highest tissue concentrations were reported in choroid+retinal pigmented epithelium and iris. High levels of radioactivity were associated with the uveal tract/retina of the partially pigmented rat, suggesting a preferential affinity for binding to melanin, in line with the *in vitro* study results.

Risdiplam was metabolically stable in human liver microsomes and hepatocytes. M1 was identified in liver microsomes and hepatocyte samples of human and animal species. M1, the major circulating metabolite in humans and monkeys, was detected in all species. The fraction of unbound risdiplam was higher in young rats and mice *in vitro*, suggesting that plasma protein binding increased with age. *In vitro*, risdiplam showed a high binding to melanin.

M1 was also formed *in vivo* following oral administration of risdiplam to male Wistar rats or cynomolgus monkeys with average exposure levels in plasma of 36.3% (rats) and 12-15% (monkeys on Day 1 and Day 3) of parent compound exposure. Plasma half-lives were 5.52 h and 4.6 h for risdiplam and M1 in rats. In monkeys, a higher exposure to risdiplam and M1 was observed on Day 3 compared to Day 1 (2.32- and 2.81-fold). *In vitro*, flavin-containing monooxygenase enzymes (FMO) 1 and 3 and CYP enzymes 3A4 and 2J2 were capable of metabolising risdiplam to M1.

^{14}C-risdiplam-related radioactivity crossed the placental barrier and was transferred into the milk of lactating rats (3.13-fold higher concentrations in milk than in plasma). The half-lives of radioactivity in

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

milk and plasma were 14.0 h and 7.68 h. The majority of radioactivity was excreted in the faeces of rats and monkeys.

Toxicology

Repeat-dose GLP toxicology studies with risdiplam were conducted in juvenile and adult rats (up to 26 weeks, with an 8-week recovery period), in juvenile monkeys (up to 39 weeks, with a 22 week recovery period), and in rasH2 transgenic mice (26-week carcinogenicity study). Oral administration route and dosing frequency were consistent with the proposed clinical use. The duration of the repeat-dose toxicology studies supports the intended chronic use in humans.

Seven pre-terminal deaths (at 7.5 mg/kg/day) occurred in rats (26-week study) due to crypt single cell necrosis and/or degeneration/necrosis in the intestinal tract and decreased cellularity in the bone marrow. Risdiplam-associated mortality also occurred in monkeys in a 2-week study in which two animals were prematurely terminated due to poor condition and weight loss at 20 mg/kg/day.
The main targets of toxicity were skin, retina, intestinal tract, testis and epididymis. In monkeys at 7.5/5 mg/kg/day, shedding/peeling skin and hair loss were frequently seen. At ≥ 3 mg/kg/day, monkeys showed retinal defects, macular degeneration and functional changes in the eye, which partially persisted after the recovery period. The exposure at the NOAEL for retina findings represents a safety margin of 1.5-fold human exposure. There were no corresponding findings in the clinical trials. Ophthalmological monitoring during treatment is included in the Risk Management Plan. Small and soft testis, small epididymis, and ocular findings were observed in pigmented rats, with a safety margin of 1.7-fold.
Risdiplam was not mutagenic in the Ames test but showed clastogenic/aneugenic activity in an *in vitro* micronucleus test and induced chromosomal aberrations in rats at an exposure corresponding to 2.9-fold the clinical exposure. In addition, increases in numbers of micronucleated immature erythrocytes were seen in juvenile rats in a 13-week study at exposures below (0.4-fold) the clinical exposure.
Risdiplam was not carcinogenic in a 26-week oral carcinogenicity study in the rasH2 mouse. The NOAEL was 9 mg/kg/day, associated with exposure margins of 12-fold (males) and 9.1-fold (females) the clinical exposure. A 2-year carcinogenicity study in rats is being conducted as a post-marketing commitment.
In an embryo-foetal development study in rabbits, the percentage of foetuses with hydrocephaly, absent accessory lung lobes and small gallbladder was increased at 12 mg/kg/day. The NOAEL for maternal toxicity and embryo-foetal development toxicity was 4 mg/kg/day (safety margin of 6.2-fold). In Wistar rats, the NOAEL for embryo-foetal toxicity and for maternal toxicity was 3 mg/kg/day (safety margin: 3.6-fold).
In the pre- and postnatal development study in Wistar rats, the length of gestation was significantly increased at 3 mg/kg/day. Risdiplam increased length of gestation at 3 mg/kg/day. In the adult F1 generation, sexual maturation (vaginal opening) was delayed at 3 mg/kg/day, and the numbers of corpora lutea, implantation sites, and live embryos were decreased at ≥ 1.5 mg/kg/day. The NOAEL for F0 maternal toxicity or their offspring was 0.75 mg/kg/day (corresponding to 0.8-fold the human exposure level).
Oral administration of risdiplam to juvenile rats from Day 22 to Day 112 postpartum at ≤ 7.5 mg/kg/day resulted in microscopic changes in the intestinal tract and male reproductive organs at 7.5 mg/kg/day. These changes were reversible, except for the ones in the testis. At 7.5 mg/kg/day, body weight gain was lower during the treatment and recovery periods. The NOAEL was 3 mg/kg/day (safety margin: 6.2-fold). Similarly, in a 4-week toxicity study in juvenile Wistar rats (up to 2.5 mg/kg/day from Day 4 to Day 31 postpartum), reduced body weight gain, reduced bone length, impaired neurobehavioural performance and delayed male sexual maturation were observed at ≥ 1.5 mg/kg/day. Risdiplam-related decreases in testis and epididymis weights were observed at ≥ 1.5 mg/kg/day, which persisted following an 8-week off-drug period. Therefore, the NOAEL was 0.75 mg/kg/day, which is associated with AUC values of 680 and 686 ng.hr/mL (safety margin: 0.53-fold) for risdiplam on postnatal day (PND) 31 in males and females. A very low incidence of nephroblastomatosis was observed in both juvenile rat studies that was related to the breeding scheme of the animals in the testing facility.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Mechanistic studies showed that risdiplam induced dose-dependent impairment of lysosomal function and an accumulation of autophagosomes in human retinal pigment epithelial cells, which were found to be associated with the peripheral photoreceptor degeneration observed in risdiplam-treated monkeys.

The submitted description of key safety findings from nonclinical studies in the RMP is considered adequate.
There is no concern with respect to excipients and impurities.
Based on the ERA, a risk for the environment is considered unlikely.

Conclusions
Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Evrysdi with the new active substance risdiplam in the proposed indication. The pharmacological properties as well as the pharmacokinetic and toxicity profiles of risdiplam were adequately characterised. Adverse effects were observed at clinically relevant exposures in several organs, which can be accepted for the indication. The low/non-existent safety margins for gastrointestinal toxicity, genotoxicity, retinal toxicity, embryo-foetal toxicity, and effects on reproductive functions are addressed adequately in the information for healthcare professionals.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Pharmacokinetics

ADME

Biopharmaceutical Development

The only risdiplam dosage form is an oral solution. No absolute or relative bioavailability studies have been conducted.

Fed administration of risdiplam resulted in a prolongation of the median tmax from 2 h to 4.5 h. Risdiplam Cmax and AUC were not affected by food. However, this conclusion was based on the data of three subjects only. The recommendation to administer risdiplam after a meal was based on the mode of administration in the Phase 3 studies.

Dose Proportionality

An approximately dose proportional increase of risdiplam Cmax and AUCinf was observed after administration of single doses between 0.6 mg and 18 mg. After once daily multiple dosing, there was a slightly less than dose proportional increase of the risdiplam and M1 (inactive main metabolite of risdiplam) Cmax and AUC between 5 mg and 8 mg (1.4-fold increase of exposure for a 1.6-fold increase of dose). However, a fully linear pop PK model described the risdiplam exposure quite well across a dose range of 0.00106 mg/kg to 18 mg.

Pharmacokinetics after multiple Dosing

Both risdiplam and M1 reached steady state within 7 to 9 days of QD dosing. An approximately 3- and 4-fold accumulation of risdiplam and M1, respectively, was observed after QD dosing. These findings were in agreement with a pharmacokinetically relevant half-life of 30 – 40 h.

Distribution

The risdiplam Vz/F was 542 L. After administration of a single dose of [^{14}C] risdiplam, the ratio between the radioactivity in blood and plasma was between 0.691 and 0.925. The risdiplam *in vitro* blood – plasma partitioning was 1.3.

The unbound fraction of risdiplam was between 11.2% and 12.8% in healthy subjects. It was barely affected by mild or moderate hepatic impairment. In mostly paediatric SMA patients, it was between 6.1% and 15.4%.

The unbound fraction of M1 was between 7.9% and 9.4% in healthy subjects. As for the parent compound, mild or moderate hepatic impairment had no major impact on the plasma protein binding of the metabolite.

These data were in good agreement with the *in vitro* plasma protein binding data. Risdiplam was bound to serum albumin only.

No age dependency of risdiplam *in vitro* plasma protein binding was observed in humans.

Metabolism - In vitro Data

Risdiplam was metabolised to M1 by both FMO1 (flavin monooxygenase) and FMO3 as well as by CYPs 1A1, 2J2, 3A4, and 3A7, with FMO and CYP3A4 as the main contributors to its metabolism. M1 was further metabolised by several CYPs and FMO enzymes, with CYP2J2, 3A4, FMO1 and FMO3 as the most active enzymes.

Compared to adults, the risdiplam metabolism to M1 was higher in children between 6 months and 12 years of age.

Metabolism - Clinical Data

After administration of a single dose of [^{14}C] risdiplam, risdiplam was the major component in plasma, accounting for 83% of drug-related material in circulation (percent of AUC0-48). M1 was identified as the major circulating metabolite and represented 14% of AUC0-48. Four additional low-level metabolites (M2, M7, M9 and M26), all resulting from biotransformation of the piperazine moiety, were observed in plasma but, relative to the AUC of total drug-related material in plasma, no individual metabolite accounted for greater than 2.2%.

In faeces, risdiplam was also the main drug-related component, accounting for 14% of the dose. M5, M7 (both resulting from biotransformation of the piperazine moiety) and M10 (carboxylic acid metabolite), were the most abundant metabolites, accounting for 3.0, 4.1 and 2.2% of dose, respectively. A number of low-level metabolites were observed in faeces (mainly involving biotransformation of the piperazine moiety), but no single component accounted for more than 1.5% of the dose.

In urine, again risdiplam was the main drug-related component, accounting for 7.7% of the dose. The most abundant metabolite was M7, accounting for 1.8% of the dose. Additional low-level metabolites were observed in urine (mainly involving biotransformation of the piperazine moiety), but no single component accounted for more than 1.0% of the dose.

The metabolite/parent ratio (AUC) after single dose administration to healthy subjects was about 20% and increased to about 30% after multiple QD dosing. In SMA patients, the mean metabolite/parent ratio was 33.7% in infants and between 27% and 30% in older patients.

Elimination
The risdiplam half-life in healthy adult subjects was about 40 h. About 4% of the administered dose was excreted as unchanged risdiplam in urine, independently of the administered dose. The M1 half-life was about 32 h.

After administration of a single dose of [^{14}C] risdiplam, 28.2% and 53.2 % of the radioactive dose were recovered in urine and faeces, respectively. Most of the radioactivity was excreted within 15 to 20 days.

Special Populations / Intrinsic Factors

There were no major pharmacokinetic and pharmacodynamic differences between healthy **Japanese** and healthy Caucasian subjects.

Mild or moderate **hepatic impairment** had no major impact on risdiplam and M1 pharmacokinetics. Risdiplam AUCinf and Cmax were approximately 20% and 5% lower, respectively, in subjects with mild hepatic impairment compared to subjects with normal function. Similar changes were observed for M1 AUCinf and Cmax.

Risdiplam AUCinf and Cmax parameters were approximately 8% and 20% higher, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. The M1 AUCinf and Cmax were unchanged.

There was a statistically significant correlation between Child Pugh score and risdiplam exposure (Cmax and AUC). This was not the case for M1.

No data are available for subjects with severe hepatic impairment.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

As renal excretion is not a major route of risdiplam elimination, and hepatic impairment had no clinically meaningful impact on risdiplam exposure, no dedicated study in subjects with **renal impairment** was conducted.

The pharmacokinetic data supported the dosing recommendations in special patient populations.

The risdiplam pharmacokinetics in SMA patients was investigated in a population pharmacokinetic analysis. The dataset included 527 subjects, of whom 61 were healthy subjects and 466 were SMA patients. The age range of the SMA patients in the dataset was 0.18 – 61 years. The dataset included 62 infants (< 1 year), 42 toddlers (1 year to < 4 years), 153 children (4 years to < 12 years), 119 adolescents (12 years to ≤ 18 years) and 90 adults (> 18 years).

The risdiplam pop PK base model included allometric scaling of the volume and clearance terms for both body weight and age.
Of the covariates investigated for their potential impact on risdiplam PK, SMA type (=> SMA patient or healthy subject), sex and AST as covariates of CL/F, SMA type 2 as covariate of Vc/F and SMA type3 as covariate of the absorption transit rate reached statistical significance in the covariate analysis. After evaluation of the clinical relevance of theses covariate effects, only SMA type as covariate of CL/F remained in the final pop PK model. Risdiplam CL/F was 56.6% higher in healthy subjects compared to SMA patients. The evaluation of the covariate effects was comprehensive and well documented. The final risdiplam pop PK model described the data well across all age groups.

The risdiplam doses of 0.2 mg/kg for patients < 2 years, 0.25 mg/kg for patients ≥ 2 years with a body weight of < 20 kg, and 5 mg for patients ≥ 2 years with a body weight of ≥ 20 kg have been selected to achieve a mean AUC0-24h,ss of 2000 ng*h/mL across all age/weight groups. This AUC value was based on the NOAEL in the animal toxicology studies. The results of the pop PK analysis demonstrated that this goal was achieved.

Interactions

EFFECT OF OTHER DRUGS ON RISDIPLAM

In vitro Data
CYP3A4 was the main CYP involved in the metabolism of risdiplam and M1, although it should be noted that CYPs played only a minor role in the metabolism of risdiplam.
Furthermore, risdiplam was a weak substrate for BCRP, but not for Pgp or OATPs. M1 was a substrate for both Pgp and BCRP.

Clinical Data

Interacting Compound	**GMR (90% CI)**
Itraconazole (strong CYP3A4 inhibitor, Pgp inhibitor)	RIS Cmax: 0.906 (0.841, 0.976) RIS $AUC_{0\text{-}120h}$: 1.11 (1.03, 1.19)

Itraconazole had no effect on risdiplam exposure. The M1 plasma concentrations were not measured in the respective interaction study. The results of the clinical interaction study were in agreement with the *in vitro* data. CYP3A4 was only one of several enzymes involved in the metabolism of risdiplam. Risdiplam was not a substrate for Pgp. Both risdiplam and M1 showed a high passive permeability *in vitro*. Therefore, the impact of efflux transporters on their exposure is likely to be low.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

EFFECT OF RISDIPLAM ON OTHER DRUGS

In vitro Data
There was no evidence of direct or time-dependent inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 at concentrations up to 12.5 µM and 10 µM of risdiplam and M1, respectively. There was a signal for direct and time-dependent inhibition of CYP3A4 by risdiplam or M1. Risdiplam and M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4 at concentrations up to 1 µM.

Risdiplam and/or M1 inhibited Pgp, BCRP, OAT1, OCT2, MATE1 and MATE2-K. Based on the static *n vivo* drug-drug interaction (DDI) risk assessment, the inhibition of MATE1 and MATE2-K could not be excluded at therapeutic exposure.

Clinical Data

Interacting Compound	**GMR (90% CI)**
Midazolam (sensitive CYP3A4 substrate)	MID Cmax: 1.16 (1.06, 1.28) MID AUCinf: 1.08 (0.93, 1.26) 1-OH-MID Cmax: 1.27 (1.14, 1.41) 1-OH_MID AUCinf: 1.12 (0.99, 1.27)

The time-dependent inhibition of CYP3A4 observed *in vitro* did not translate into a clinically relevant effect of risdiplam on midazolam exposure *in vivo*. Based on physiologically based pharmacokinetic simulations, an interaction of similar magnitude was expected in children between 2 months and 18 years of age.

The *in vitro* and pharmacokinetic data supported the dosing recommendations regarding interactions.

Pharmacodynamics

Mechanism of Action and primary Pharmacology

Risdiplam caused a dose/concentration-dependent increase in the SMN2 full-length over SMNΔ7 mRNA ratio, consistent with its proposed mechanism of action. However, in healthy subjects, this did not translate into an increase of SMN protein.

The effect on the SMN2 full-length over SMNΔ7 mRNA ratio was also observed in SMA patients. The steep, risdiplam concentration-dependent increase of this ratio was mainly due to a decrease of the SMNΔ7 mRNA rather than an increase of the SM2 full-length mRNA. At the targeted exposure of an AUC0-24h,ss of 2000 ng*h/mL, a 75% decrease of SMNΔ7 mRNA from baseline was estimated.

In contrast to healthy subjects, the risdiplam effect on the SMN2 full-length over SMNΔ7 mRNA ratio translated into a concentration-dependent increase of SMN protein in SMA patients. At therapeutic exposure, a 2- to 3- fold increase from baseline was observed.

Secondary Pharmacology (Safety)

Impact on QTc

The results of two exposure-response analyses indicated that risdiplam did not cause a QTcF prolongation at therapeutic exposure. For the time being, no data at supra-therapeutic exposure are available.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6.2 Dose Finding and Dose Recommendation

Dose finding was performed in both parts 1 of the two pivotal studies FIREFISH and SUNFISH.
In part 1 of the FIREFISH study, a total of 21 patients with SMA type 1 were included. Median age at diagnosis was 3 months, symptoms onset was between 0.9 and 3 months, and two copies of the SMN2 gene were detected in all patients. Based on the pharmacokinetic (PK) and pharmacodynamic (PD) results (increase of SMN protein), doses of 0.2 mg/kg body weight for patients up to 2 years and 0.25 mg/kg body weight for patients over 2 years were identified as suitable doses for part 2 of the study.
In part 1 of the SUNFISH study, 51 patients were included, of whom n = 31 were in the age group between 2-11 years and n = 20 in the age group between 12-25 years. Type 2 SMA was diagnosed in 72.5% of the patients; 3 SMN2 copies were detected in 90% of the total study population. The time between the first symptoms of SMA and the start of therapy with risdiplam was given as an average of 106 months. Based on the PK and PD results of part 1, a dose of 0.25 mg/kg was used for patients with SMA type 2 and 3 with a weight < 20 kg and a fixed dose of 5 mg per day for patients with a weight ≥ 20 kg was defined.

6.3 Efficacy

Study BP39056 (FIREFISH)
Study BP39056 (FIREFISH) was an open-label single-arm study in infants with genetically confirmed SMA type 1. In view of the rapid clinical deterioration, the significantly reduced life expectancy and the clearly defined natural disease course in patients with SMA type 1, no placebo control group was used in this study. On the basis of published data on the natural course of untreated patients with SMA type 1, certain (motor) goals and survival rates were predefined for the efficacy parameters. While part 1 of this study was designed for dose finding, efficacy was assessed in part 2.
Sitting without assistance for at least 5 seconds was defined as the primary endpoint. Secondary endpoints were the proportion of patients with a CHOP-INTEND score of > 40 or an improvement of 4 compared to baseline, the achievement of certain milestones according to Hammersmith Infant Neurological Examination Module 2 (HINE-2), survival without permanent ventilation, the proportion of patients who swallowed and could be fed orally and the frequency of hospitalisations. Patients from part 1 of the study (dose finding) did not participate in part 2.
A total of 41 patients with SMA type 1 were included in Part 2 of the FIREFISH study (characteristics: 54% female, median age at the start of the study 5.3 months (range 2.2 to 6.9 months), median age at diagnosis 2.8 months, onset of symptoms between 1 and 3 months, two copies of the SMN2 gene were detected in all patients). At the 12-month analysis, there were still 38 patients in the ongoing study with a median of 15 months (range 1.6 to 20.1 months). Three patients died due to SMA-associated respiratory insufficiency. In the baseline examination, the median CHOP-INTEND score was 22 points (range 8 to 37), the median HINE-2 score was one point (range 0 to 5) and the median compound muscle action potential (CMAP) amplitude was 0.2 mV.
After a treatment period of 12 months, 29.3% of the patients with SMA type I were able to sit for at least 5 seconds without help. Around 56% of the patients achieved a CHOP-INTEND score of at least 40 points, while an increase in the score of at least 4 points was demonstrated in 90% of the patients. The median CHOP-INTEND score in the included population was 22. Using the HINE-2 assessments, 78% of the patients were classified as “milestone responders”. In 85% of the patients, the creation of a tracheostomy and/or non-invasive ventilation of at least 16 hours per day or intubation for longer than 21 days without a specific trigger (e.g. an infection) was not necessary after 12 months. Around 93% of the patients were still alive at the end of the study. These effects of risdiplam in SMA type 1 patients (with symptoms onset within the first 3 months of life and treatment started within the first 7 months of life) can be regarded as clinically relevant.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Study BP39055 (SUNFISH)
Study BP39055 (SUNFISH) was designed to include a broad sample of patients with type 2 and 3 SMA, representative both in age and disability status of patients seen in clinical practice. Patients with SMA type 4 were not included. While part 1 of this study was designed for dose finding, efficacy was assessed in part 2 in a randomised, placebo-controlled design.
The change in the motor function measure 32 (MFM32) score at 12 months compared to baseline was defined as the primary endpoint. Secondary endpoints were the change in MFM32 of at least 3 points compared to baseline, the proportion of patients with stabilisation or improvement in MFM32, change in revised upper limb module (RULM) and Hammersmith Functional Motor Scale Expanded (HFMSE) scores compared to baseline, change in forced vital capacity (FVC) and the subjective assessment of the treatment patients and their caretakers.
A total of 211 non-ambulatory patients with type 2 and type 3 SMA were screened and 180 patients were included in the study (2:1 verum: placebo). The median age was 9 years. Around 31% of the patients were younger than 6 years, 12% older than 18 years. The gender ratio was balanced across the different treatment groups. In 87% of the total population there were 3 copies of the SMN2 gene, and a type 2 SMA was diagnosed in 71%. The age at first onset was around 12.4 months (median), the time between disease manifestation and the start of treatment was around 103 months (median). Overall, 67% of the patients had scoliosis. At the time of inclusion in the study, the median MFM32 was around 48, the RULM was around 19 and the HFMSE was at 13/14.
In the active risdiplam group, after a treatment period of 12 months, a mean increase in the MFM32 score of 1.36 was detected, compared to a deterioration of -0.19 ($p = 0.016$) in the placebo group. The secondary endpoints showed small but statistically significant differences in the proportion of patients with an improvement in MFM32 by at least 3 points (38.3% vs. 23.7%) or > 0 points (69.6% vs. 54.2) and also in the change in RULM compared to baseline. No statistically significant effect of risdiplam on FVC could be demonstrated. In the Caregiver- and Patient-reported SMA Independence Scale, higher numerical values were achieved in the active group, but these were not significantly different from the placebo group. The effects of risdiplam in patients with SMA type 2 and 3 were less pronounced compared to the effects in the SMA type 1 study but are still regarded as clinically relevant.

For further details, please see the “Properties/effects” and “Clinical efficacy” sections of the information for healthcare professionals

6.4 Safety

The most commonly observed (>10%) adverse events in the clinical studies in SMA type 1 and also in SMA type 2 and 3 patients were upper respiratory tract infections, pyrexia, headache, diarrhoea and rash. While serious adverse events like pneumonia, bacteraemia, and influenza occurred more frequently in the risdiplam group than the placebo group in the SUNFISH study, these differences were based on small numbers, and such events are commonly seen in SMA patients. Six cases of death occurred in the open-label FIREFISH study in infants with SMA type 1, which were caused by respiratory complications and can most probably be attributed to the underlying SMA disease. The safety profile of risdiplam in non-treatment-naïve patients in another ongoing study (JEWELFISH) was consistent with the safety profile in treatment-naïve SMA patients (FIREFISH and SUNFISH).
No prohibitive safety signals occurred during the observation period in the clinical studies. The effects on retinal structure, epithelial tissue and haematological parameters that were found in preclinical investigations have not yet been observed in clinical studies with SMA. However, the available clinical safety data are limited with regard to the number of patients exposed and the length of exposure to risdiplam.

For further details, please see the “Undesirable effects” and the “Warnings and precautions” sections of the information for healthcare professionals.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Conclusions: Clinical Assessment

Risdiplam showed clinically relevant effects in patients with SMA type 1 and SMA type 2 / 3 in two adequate clinical trials. Based on the available safety data, no prohibitive safety signals were identified. Overall, the ratio of benefits to risks in the treatment of patients 2 months of age and older with 5q-associated spinal muscular atrophy is considered favourable.

Conclusions: Clinical Pharmacology

There were no major pharmacokinetic/pharmacodynamic issues associated with risdiplam.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Evrysdi, powder for oral solution, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Evrysdi®

Composition

Active substances

Risdiplam.

Excipients

Mannitolum, isomaltum (E953) 2.97 mg/1 ml, acidum tartaricum, natrii benzoas (E211) 0.38 mg/1 ml, macrogolum 6000, sucralosum, acidum ascorbicum, dintarii edetas, strawberry aroma, maltodextrinum et modified starch (E1450).

80 ml of prepared Evrysdi solution contains 7,2 mg sodium.
1 ml ready to use solution contains 0,09 mg sodium.

Pharmaceutical form and active substance quantity per unit

Evrysdi 0,75 mg/ml powder for oral solution is yellowish to greenish, yellow greyish. The powder is contained in a brown glass bottle. One bottle contains 60 mg risdiplam in 2 g powder. After preparation of the oral solution with purified water or water for injection, the final volume is 80 ml. 1 ml solution contains 0,75 mg risdiplam (see section "Other instructions", Instructions for handling).

Indications/Uses

Evrysdi is indicated for the treatment of 5q-associated spinal muscular atrophy (SMA) in patients 2 months of age and older.

Dosage/Administration

Evrysdi oral solution must be prepared by a medical professional (e.g. physician or pharmacist) prior to being dispensed.

It must be ensured that a medical professional discusses with the patient or carer how the prescribed daily dose is to be prepared and taken, before the first dose is administered (see “Other Information” section, Information for handling).
Initiation and monitoring of treatment with Evrysdi must be undertaken by physicians experienced in diagnosing and treating patients with spinal muscular atrophy.

The clinical development programme did not include type IV SMA patients.

Usual dosage

Evrysdi is taken or given once a day, at approximately the same time each day, using the reusable syringes for oral administration provided in the pack.
The recommended once daily dose of Evrysdi for the treatment of SMA is determined by age and body weight of the patient (see Table 1).

Table 1: Dosing Regimen by Age and Body Weight

Age and Body Weight	***Recommended Daily Dose***
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

Dose changes must be made under the supervision of a healthcare professional. Treatment with a daily dose above 5 mg has not been studied to date. No data are available in infants below 2 months of age.

Patients with impaired hepatic function

No dose adjustment is required in patients with mild or moderate hepatic impairment. Evrysdi has not been studied in patients with severe hepatic impairment (see section “Pharmacokinetics”, Kinetics in specific patient groups).

Patients with impaired renal function

The safety and efficacy of Evrysdi in patients with renal impairment have not been studied. No dose adjustment is expected to be required in patients with renal impairment (see section “Pharmacokinetics”, Kinetics in specific patient groups).

Elderly patients

Clinical studies of Evrysdi did not include patients aged 65 years and over, therefore, it was not determined whether they respond differently to the medication than younger patients.

Children and adolescents

The safety and efficacy of Evrysdi in paediatric patients under 2 months of age have not yet been established (see section “Pharmacokinetics”, Clinical efficacy).

Delayed administration

Evrysdi is taken orally once daily at approximately the same time each day. If a dose of Evrysdi is missed, it should be taken as soon as possible if still within 6 hours of the scheduled dose. Otherwise, skip the missed dose and take the normal dose at the regularly scheduled time the next day.
If a dose is not fully swallowed or vomiting occurs after taking Evrysdi, do not administer another dose to make up for the incomplete dose. Wait until the next day to administer the next dose at the regularly scheduled time.

Mode of administration

For the administration of the daily dose of Evrysdi, the reusable syringe for oral administration contained in the package should be used.

Selecting the appropriate reusable oral syringe for the prescribed daily dose

Table 2: Selecting the appropriate syringe for oral administration of the prescribed daily dose of Evrysdi

Syringe Size	Dosing Volume	Syringe Increments
6 ml	1,0 ml to 6,0 ml	0,1 ml
12 ml	6,2 ml to 6,6 ml	0,2 ml

For the calculation of dosing volume, the volume increments of the oral syringe also need to be considered. The dose volume is rounded up or rounded down to the closest volume increment marked on the selected oral syringe (e.g. 6,3 ml to 6,4 ml, 3,03 ml to 3,0 ml and 1,05 to 1,1 ml).

The patient should take the Evrysdi solution immediately after it is drawn up into the reusable oral syringe. If the content of the syringe is not taken or administered within 5 minutes, the dose should be discarded (see section “Disposal of unused/expired medicines”) and a new dose should be prepared.

Evrysdi should be administered after a meal. The patient should drink some water after taking Evrysdi to ensure the medication has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube, administer Evrysdi via the tube. The tube should be flushed with water after delivering Evrysdi (see section ”Other Information”, Instructions for handling).

Contraindications

Evrysdi is contraindicated in patients with a known hypersensitivity to risdiplam or any of the excipients.

Warnings and precautions

General
In animal studies, retinal changes, epithelial changes, particularly of the skin and the gastrointestinal tract, and indications of bone marrow toxicity (changes to complete blood count) were observed. The risk that such changes may also occur in humans cannot be conclusively assessed at present due to limited long-term safety data.

Embryo-foetal Toxicity
Embryo-foetal toxicity has been observed in animal studies (see section “Preclinical data”). Patients of reproductive potential should be informed of the risks and must use highly effective contraception during treatment and for at least 1 month after the last dose of Evrysdi in female patients, and 4 months after the last dose of Evrysdi in male patients. (see section “Dosage/Administration”).

Potential Effects on Male Fertility
Due to reversible effects of Evrysdi on male fertility based on observations from animal studies, male patients should not donate sperm while on treatment and for 4 months after the last dose of Evrysdi (see section “Pharmacokinetics”, Kinetics in specific patient groups and section Preclinical data).

Skin contact with the powder and reconstituted oral solution is to be avoided. However, if the medicinal product (powder or solution) gets on the skin, the area should be washed with water and soap.

This medicinal product contains 0,38 mg sodium benzoate per 1 ml. This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is nearly "sodium-free".

This medicinal product contains isomaltol. Patients with the rare hereditary fructose intolerance should not use this medicine.

Interactions

Effects of Evrysdi on other medicinal products

In vitro risdiplam and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4. *In vitro* risdiplam and M1 did not inhibit (reversible or time-dependent inhibition) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6) with the exception of CYP3A. Risdiplam is a weak inhibitor of CYP3A. In healthy adult subjects, administration of Risdiplam once daily for 2 weeks slightly increased the exposure of midazolam, a highly sensitive CYP3A substrate (AUC 11%; Cmax 16%). The extent of this interaction is not considered clinically relevant, and therefore no dose adjustment is required for CYP3A substrates. Based on physiologically based pharmacokinetic (PBPK) modelling, a similar magnitude of this effect is expected in children and infants starting at 2 months of age.

In vitro studies have shown that risdiplam and its major metabolite are not significant inhibitors of human MDR1, organic anion-transporting polypeptides (OATP) 1B1, OATP1B3, as well as organic anion transporters 1 and 3 (OAT 1 and 3). Risdiplam and its metabolite are, however, *in vitro* inhibitors of the human organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion (MATE)1 and MATE2-K transporters. At therapeutic active substance concentrations, no interaction is expected with OCT2 substrates. The effect of co-administration of risdiplam on the pharmacokinetics of MATE1 and MATE2-K substrates in human is unknown. Based on *in vitro* data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K [see Pharmacokinetics], such as metformin (see section “Pharmacokinetics”). If co-administration cannot be avoided, drug-related toxicities should be monitored and dosage reduction of the co-administered active substance should be considered if needed.

Effects of other medicinal products on Evrysdi

Risdiplam is primarily metabolized by flavin monooxygenase 1 and 3 (FMO1 and 3), and also by CYP isoenzymes 1A1, 2J2, 3A4 and 3A7. Risdiplam is not a substrate of human multidrug resistance protein 1 (MDR1).

Co-administration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 6 mg risdiplam did not exhibit a clinically significant effect on the pharmacokinetics (PK) of risdiplam (11% increase in AUC, 9% decrease in Cmax). No dose adjustments are required when Evrysdi is co-administered with a CYP3A inhibitor.
No drug-drug interactions are expected via the FMO1 and FMO3 signal pathway.

Pregnancy, lactation

Male fertility may be compromised while on treatment with Evrysdi based on preclinical study results. In rat and monkey reproductive organs, sperm degeneration and reduced sperm numbers were observed (see section “Preclinical data”).

Prior to initiating treatment with Evrysdi, fertility preservation strategies should be discussed with male patients who are to receive Evrysdi. Male patients may consider sperm preservation prior to treatment initiation. Male patients who wish to father a child should stop treatment with Evrysdi for a minimum of 4 months (see section Warnings and Precautions).

Based on preclinical study results, an impact of Evrysdi on female fertility is not expected (see section “Preclinical data”).

The pregnancy status of females of reproductive potential should be verified prior to initiating Evrysdi therapy.

Male and female patients of reproductive potential should adhere to the following contraception requirements:

- Male patients and their female partners, if they are of childbearing potential, should use highly effective contraception during treatment with Evrysdi and for at least 4 months after the last dose.
- Female patients of childbearing potential should use highly effective contraception during treatment with Evrysdi and for at least 1 month after the last dose.

Pregnancy

There are no clinical data from the use of Evrysdi in pregnant women.

Risdiplam has been shown to be embryo-foetotoxic and teratogenic in animal studies. Based on the findings from animal studies, risdiplam crosses the placental barrier and may cause foetal harm (see section “Preclinical data”).

Evrysdi should not be used during pregnancy unless this is clearly required. If a pregnant woman needs to be treated with Evrysdi, she should be clearly advised on the potential risk to the foetus.

Lactation

It is not known whether Evrysdi is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk (see section “Preclinical data”). As the potential for harm to the nursing infant is unknown, a decision must be made with the patient’s treating physician. It is recommended not to breastfeed during treatment with Evrysdi.

Effects on ability to drive and use machines

The effect of Evrysdi on driving ability or the ability to operate machinery has not been investigated in appropriate studies.

Undesirable effects

The following definitions have been used to classify the frequency of adverse drug reactions: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (not estimable based on available data).

Summary of the safety profile

In infantile-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical trials were pyrexia (48.4%), rash (27.4%) and diarrhoea (16.1%). In later-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical trials were pyrexia (21.7%), diarrhoea (16.7%) and rash (16.7%).
The adverse reactions mentioned above occurred without an identifiable clinical or temporal pattern and generally resolved despite ongoing treatment in infantile-onset and later-onset SMA patients.

Table 3: Summary of adverse drug reactions for infantile-onset and later-onset SMA patients observed in Evrysdi clinical trials

System Organ Class	Infantile-onset SMA[2] (Type 1)	Later-onset SMA[3] (Type 2 and 3)
Gastrointestinal Disorders		
Diarrhoea	Very common	Very common
Mouth and aphthous ulcers	Common	Common
Skin and Subcutaneous Tissue Disorders		
Rash[1]	Very common	Very common
General Disorders and Adminstration Site Conditions		
Pyrexia (including hyperpyrexia)	Very Common	Very Common
Infections and infestations		
Urinary tract infection (including cystitis)	Common	Common
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	Not Applicable	Common

1 Includes rash, maculo-papular rash, erythema, dermatitis, allergic dermatitis, papular rash, folliculitis

2 For infantile-onset SMA patients (FIREFISH Part 1 and 2), adverse reactions are defined as events which occurred in 2% of patients or more and where a causal association with Evrysdi is possible.

3 For later-onset SMA patients (SUNFISH Part 2), adverse reactions are defined as events which occur at least 2% more frequently in patients treated with Evrysdi compared to placebo during the double-blind placebo controlled period and where a causal association with Evrysdi is possible.

The available safety data are limited in terms of the number of patients exposed to Evrysdi and the length of exposure. There may be potential, relatively rare and potentially serious adverse drug reactions (ADRs) that were undetected during the study programme.

Safety profile in Patients Previously treated for SMA

The safety profile of Evrysdi for non-naive patients in the JEWELFISH study is consistent with the safety profile for treatment naive SMA patients treated with Evrysdi in the FIREFISH (Part 1 and Part 2) and SUNFISH (Part 1 and Part 2) studies. In the JEWELFISH study, 76 patients previously treated with nusinersen and 14 patients previously treated with onasemnogene abeparvovec were enrolled (see section “Properties/Effects”, Clinical efficacy).

Non-clinical effects

The non-clinical effects on retinal structure, epithelial tissue and haematological parameters described in the section "Preclinical data" have not been observed to date in Evrysdi clinical studies with SMA.

QT Prolongation

A pharmacokinetic/pharmacodynamic analysis showed no evidence of QTc prolongation caused by Evrysdi with exposure in the therapeutic range, but there are no corresponding data at exposure greater than therapeutic levels.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious side effect online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no experience with overdosage of Evrysdi in clinical trials. There is no known antidote for overdosage of Evrysdi. In case of overdosage, the patient should be closely monitored and supportive care instituted.

Properties/Effects

ATC code

M09AX10

Mechanism of action

Risdiplam is a splicing modifier of SMN2 pre-mRNA (survival of motor neuron 2) for the treatment of SMA which is caused by an SMN protein deficiency as a result of mutations in chromosome 5q. Functional SMN protein deficiency is the pathophysiological mechanism of all SMA types. Risdiplam corrects the splicing of SMN2 and shifts the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript leading to an increased production of functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein concentrations.

Pharmacodynamics

Risdiplam distributes evenly to all parts of the body, including the central nervous system (CNS) by crossing the blood brain barrier, and thereby leading to SMN protein increase in the CNS and throughout the body. Concentrations of risdiplam in plasma and SMN protein in blood reflect its distribution and pharmacodynamic effects in tissues such as brain and muscle.

In all clinical trials, risdiplam led to a consistent and durable increase in SMN protein with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation as measured in blood. This increase in SMN protein was sustained throughout the treatment period of up to 2 years for infantile-onset SMA and later-onset SMA patients (see section “Properties/Effects” Clinical efficacy).

Clinical efficacy

The efficacy of Evrysdi for the treatment of SMA patients with infantile-onset and later-onset SMA was evaluated in two pivotal clinical studies, FIREFISH and SUNFISH, and supported by additional data from the JEWELFISH study.

Long-term efficacy for up to two years of treatment has been demonstrated in clinical studies. Beyond two years, only limited data are available.

Infantile-onset SMA

Study BP39056 (FIREFISH) is an open-label, 2-part study to investigate the efficacy, safety, PK and pharmacodynamics (PD) of Evrysdi in symptomatic type 1 SMA patients (all patients had genetically confirmed disease with 2 copies of the SMN2 gene). Part 1 of FIREFISH was designed as the dose-finding part of the study. The confirmatory part 2 of the FIREFISH study assessed the efficacy of Evrysdi at the therapeutic dose selected based on the results from part 1 (see section “Dosage/Administration”). Patients from part 1 did not take part in part 2.

In parts 1 and 2, the key efficacy endpoint was the ability to sit without support for at least 5 seconds, as measured by Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale, after 12 months of treatment with Evrysdi.

FIREFISH part 2

In FIREFISH part 2, 41 patients with type 1 SMA were enrolled. The median age of onset of clinical signs and symptoms of Type 1 SMA was 1,5 months (1,0-3,0 months); 54% were female; 54% Caucasian and 34% of Asian descent. The median age at enrolment was 5,3 months (2,2-6,9 months) and the median time between onset of symptoms and first dose was 3,4 months (1,0-6,0 months). At baseline, the median CHOP-INTEND score was 22.0 points (8,0-37,0) and the median HINE-2 score was 1,0 (0,0-5,0).

The primary endpoint was the proportion of patients with the ability to sit without support for at least 5 seconds after 12 months of treatment (BSID-III gross motor scale, Item 22). The efficacy endpoints of Evrysdi treated patients were compared to similar cohorts of untreated patients with natural disease course (defined as performance criteria) as shown in Table 4.

Table 4: Summary of Key Efficacy Results at Month 12 (FIREFISH Part 2)

Efficacy Endpoints	Proportion of Patients N=41 (90% CI)
Motor Function and Development Milestones	
BSID-III: sitting without support for at least 5 seconds p-value based on performance criterion defined as 5%[a]	29,3% (17,8%; 43,1%) <0,0001
CHOP-INTEND: score of 40 or higher p-value based on performance criterion defined as 17%[a]	56,1% (42,1%; 69,4%) <0,0001
CHOP-INTEND: increase of ≥4 points from baseline p-value based on performance criterion defined as 17%[a]	90,2% (79,1%; 96,6%) <0,0001
HINE-2: motor milestone responders[b] p-value based on performance criterion defined as 12%[a]	78,0% (64,8%; 88,0%) <0,0001
Survival and Event-Free Survival	
Event-Free Survival[c] p-value based on performance criterion defined as 42%[a]	85,4% (73,4%; 92,2%) <0,0001
Survival p-value based on performance criterion defined as 60%[a]	92,7% (82,2%; 97,1%) 0,0005
Feeding	
Ability to feed orally[d]	82,9% (70,3%; 91,7%)

Abbreviations: CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 = Module 2 of the Hammersmith Infant Neurological Examination.

[a] p-values for survival and event-free survival are based on a Z-test; p-values for all other endpoints (BSID-III, CHOP-INTEND, HINE-2) are based on an exact binomial test. Survival proportions estimated using Kaplan-Meier methodology.

[b] According to HINE-2: Response in this analysis is defined as ≥2 point increase [or highest possible score] in ability to kick, OR ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening.

[c] An event corresponds to the endpoint of permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Three patients met the endpoint of permanent ventilation before Month 12. All three patients achieved an increase of at least 4 points in their CHOP-INTEND score compared to baseline.

[d] Includes patients who were fed exclusively orally (a total of 28 patients) and those who were fed orally in combination with a feeding tube (a total of 6 patients) at Month 12.

After 12 months of treatment with Evrysdi, 29% (12/41) of patients met the criteria for sitting without support (BSID-III, Item 22), 93% (38/41) of patients were alive, and 85% (35/41) of patients were alive and event-free (without permanent ventilation). These results indicate a clinically significant deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age.

FIREFISH Part 1

The efficacy of Evrysdi in Type 1 SMA patients is also supported by results from FIREFISH Part 1. For the 21 patients from Part 1, the baseline characteristics were consistent with symptomatic patients with Type 1 SMA. The median age at enrolment in the study was 6,7 months (3,3-6,9

months) and the median time between onset of symptoms and first dose was 4.0 months (2,0-5,8 months).
A total of 17 patients received the therapeutic dose of Evrysdi (the dose selected for Part 2). After 12 months of treatment, 41% (7/17) of these patients were able to sit independently for at least 5 seconds (BSID-III, Item 22). After 24 months of treatment, 3 more patients receiving the therapeutic dose were able to sit independently for at least 5 seconds, leading to a total of 10 patients (59%) achieving this motor milestone.

After 12 months of treatment, 90% (19/21) of patients were alive and event-free (without permanent ventilation) and reached 15 months of age or older. After a minimum of 24 months of treatment, 81% (17/21) of patients were alive and event-free and reached an age of 28 months or older (median 32 months; range 28 to 45 months), see Figure 1. Three patients died during treatment and one patient died 3,5 months after discontinuing treatment.

Later Onset SMA

Study BP39055 (SUNFISH), is a 2-part, multicentre trial to investigate the efficacy, safety, PK and PD of Evrysdi in SMA Type 2 or Type 3 patients between 2-25 years of age. Part 1 was the dose-finding portion and part 2 was the randomized, double-blind, placebo-controlled confirmatory portion. Patients from part 1 did not take part in part 2.

The primary endpoint was the change from baseline score at Month 12 on the Motor Function Measure-32 (MFM32). The MFM32 has the ability to assess a wide range of motor function across a broad range of SMA patients. The total MFM32 score is expressed as a percentage (0 to 100) of the maximum possible score, with higher scores indicating greater motor function. The MFM32 measures motor function abilities that relate to important daily functions. Small changes in motor function can result in meaningful gain or loss of daily functional ability.

SUNFISH Part 2

SUNFISH Part 2 is the randomized, double-blinded, placebo-controlled portion of the SUNFISH study in 180 non-ambulant patients with type 2 (71%) or type 3 (29%) SMA. Patients were randomized at a 2:1 ratio to receive either Evrysdi at the therapeutic dose (see section “Dosage/Administration”) or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years).
The median age of patients at the start of treatment was 9,0 years old (2-25 years old), the median time between onset of initial SMA symptoms to first treatment was 102,6 (1-275) months. Of the 180 patients included in the trial, 51% were female, 67% were Caucasian and 19% were of Asian descent. At baseline, 67% of patients had scoliosis (32% of patients with severe scoliosis). Patients had a

mean baseline MFM32 score of 46,1 and mean Revised Upper Limb Module (RULM) score of 20,1. The overall baseline demographic characteristics were well balanced between the Evrysdi and placebo groups with the exception of an imbalance of patients with scoliosis (63,3% of patients in the Evrysdi arm and 73,3% of patients in the placebo group).

The primary analysis for SUNFISH Part 2, the change from baseline in MFM32 total score at Month 12 showed a clinically meaningful and statistically significant difference between patients treated with Evrysdi and placebo. The results of the primary analysis and key secondary endpoints are summarised in Table 5 and Figure 1.

Table 5: Summary of Efficacy Results in Patients with Later-Onset SMA at Month 12 of Treatment (SUNFISH Part 2)

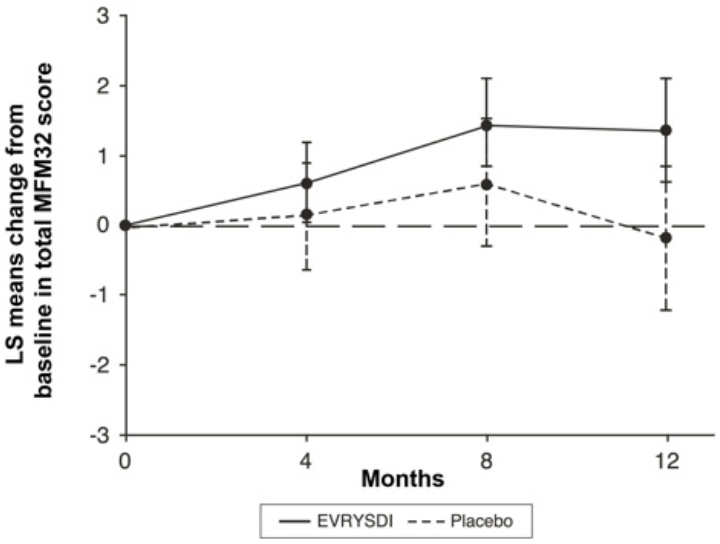
Endpoint	**Evrysdi (N = 120)**	**Placebo (N = 60)**
Primary Endpoint:		
Change from baseline in MFM32 total score[1] at Month 12 LS Mean (95%, CI)	1,36 (0,61; 2,11)	-0,19 (-1,22; 0,84)
Difference from Placebo Estimate (95% CI) p-value[2]	1,55 (0,30; 2,81) 0,0156	
Secondary Endpoints		
Proportion of patients with a change from baseline in MFM32 total score[1] of 3 or more at Month 12 (95% CI)	38,3% (28,9; 47,6)	23,7% (12,0; 35,4)
Odds ratio for overall response (95% CI) Adjusted (unadjusted) p-value[3,4]	2,35 (1,01; 5,44) 0,0469 (0,0469)	
Change from baseline in RULM total score[5] at Month 12 LS Mean (95% CI)	1,61 (1,00; 2.22)	0,02 (-0,8; 0,87)
Difference from Placebo, estimate (95% CI) Adjusted (unadjusted) p-value[2,4]	1,59 (0,55; 2,62) 0,0469 (0,0028)	

LS=least squares
[1] Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (Evrysdi n=115; placebo control n=59).
[2] Data analysed using a mixed model with repeated measurements with baseline total score, treatment, visit, age group, treatment-by-visit and baseline value-by-visit.
[3] Data analysed using logistic regression for baseline total score, treatment and age group.
[4] The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint. Unadjusted p-value was tested at the 5% significance level.
[5] Based on the missing data rule for RULM, 3 patients were excluded from the analysis (Evrysdi n=119; placebo control n=58).

Upon completion of 12 months of treatment, 117 patients continued to received Evrysdi. At the time of the 24 month analysis, these patients who were treated for 24 months experienced further

improvement in motor function between month 12 and month 24. The mean change from baseline for MFM32 was 1,83 (CI: 0.74-2.92) and for RULM was 2,79 (CI: 1,94-3,64).

Figure 1: Mean Change (LS) from Baseline in Total MFM32 Score Over 12 months in SUNFISH Part 2



* Error bars denote the 95% confidence interval.
† The MFM total score was calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100).

SUNFISH Part 1

The efficacy of Evrysdi in later-onset SMA patients is also supported by results from Part 1, the dose-finding part of SUNFISH. In part 1, 51 patients with type 2 and 3 SMA (including 7 ambulatory patients) between 2 to 25 years old were enrolled. After one year of treatment at the therapeutic dose (the dose selected for part 2), there was a clinically significant improvement in motor function as measured by MFM32 with a mean change from baseline of 2,7 points (95% CI: 1,5; 3,8). The improvement in MFM32 was maintained up to two years on Evrysdi treatment (mean change of 2,7 points [95% CI: 1,2; 4,2]).

In an exploratory analysis, the motor function assessed by MFM was compared between SUNFISH part 1 and a historical cohort with natural disease progression (weighted based on key prognostic factors). The MFM total change from baseline after 1 year and 2 years was greater in patients receiving Evrysdi compared to the natural course cohort (after 1 year: 2,7 point difference; p< 0.0001; after two years; 4,0 point difference; p< 0.0001). The natural course cohort experienced a decline in motor function as expected based on the natural progression of SMA (mean change after 1 year: -0,6 points; after 2 years: -2,0 points).

Use in previously treated SMA patients

Study BP39054 (JEWELFISH) is a single arm, open-label study to investigate the safety, tolerability, PK and PD of Evrysdi in patients with infantile-onset and later-onset SMA between 6 months and 60 years of age, who previously received treatment with other SMA therapies (including nusinersen and onasemnogene abeparvovec). As of 31 July 2020, of the 173 patients that received Evrysdi, 76 patients were previously treated with nusinersen (9 patients with Type 1 SMA, 43 with Type 2 SMA and 24 with Type 3 SMA) and 14 patients were previously treated with onasemnogene abeparvovec (4 patients with type 1 SMA and 10 with type 2 SMA).

Patients had on average a greater than 2-fold increase in SMN protein levels compared to baseline after 4 weeks of Evrysdi treatment.

Pharmacokinetics

Pharmacokinetic parameters for risdiplam have been characterized in healthy adult subjects and in patients with SMA.

After administration of Evrysdi as an oral solution, the PK of risdiplam were approximately linear between 0,6 and 18 mg. The PK of risdiplam is best described by a population PK model with resorption via three transit compartments, two-compartment disposition and elimination with first-order kinetics. Body weight and age were found to have significant effects on the PK.

The estimated exposure (mean AUC0-24h) for infantile-onset SMA patients (age 2-7 months at enrolment) at the therapeutic dose of 0,2 mg/kg once daily was 1930 ng.h/ml. The estimated exposure for later-onset SMA patients (2-25 years old at enrolment) in the SUNFISH study (part 2) at the therapeutic dose (0,25 mg/kg once daily for patients with a body weight <20 kg; 5 mg once daily for patients with a body weight ≥20 kg) was 2070 ng.h/ml. The observed maximum concentration (mean Cmax) was 194 ng/ml at 0,2 mg/kg in FIREFISH and 120 ng/mL in SUNFISH part 2.

Absorption

Risdiplam was rapidly absorbed in the fasted state with a plasma tmax ranging from 1 to 4 hours after oral administration.

In the clinical studies, risdiplam was administered with a morning meal or after breastfeeding.

Distribution

The population pharmacokinetic parameter estimates were 98 l for the apparent central volume of distribution, 93 l for the peripheral volume, and 0,68 l/hour for the inter-compartmental clearance.

Risdiplam is predominantly bound to serum albumin, without any binding to alpha-1 acid glycoprotein, with a free fraction of 11%.

Metabolism

Risdiplam is primarily metabolized by flavin monooxygenases 1 and 3 (FMO1 and FMO3), and also by CYP isoenzymes 1A1, 2J2, 3A4 and 3A7. Parent drug was the major component found in plasma, accounting for 83% of active substance related material in circulation. The pharmacologically inactive metabolite M1 was identified as the major circulating metabolite.

Elimination

Population PK analyses estimated an apparent clearance (CL/F) of 2,6 l/h for risdiplam. The effective half-life of risdiplam was approximately 50 hours in SMA patients.

Approximately 53% of the dose (14% in the form of unaltered risdiplam) was excreted in the feces and 28% in urine (8% as unaltered risdiplam).

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the PK of risdiplam. After administration of 5 mg risdiplam, the mean ratios for Cmax and AUC were 0,95 and 0,80 in mild (n=8) and 1,20 and 1,08 in moderate hepatically impaired subjects (n=8) versus matched healthy controls (n=10). The safety and PK in patients with severe hepatic impairment have not been studied to date.

Renal impairment

No studies have been conducted to investigate the PK of risdiplam in patients with renal impairment. Elimination of risdiplam as unchanged entity via renal excretion is minor (8%).

Elderly patients

No dedicated studies have been conducted to investigate the PK of Evrysdi in patients with SMA above 60 years of age. Patients with SMA up to 60 years of age were included in the JEWELFISH study. Subjects without SMA up to 69 years of age were included in clinical PK studies.

Children and adolescents

Body weight and age were identified as covariates in the population PK analysis. The dose is therefore adjusted based on age (below and above 2 years) and body weight (up to 20 kg) to obtain

similar exposure across the age and body weight range. No data are available in patients less than 2 months of age.

Ethnic origin

The PK of risdiplam does not differ in person of Japanese and Caucasian descent.

Preclinical data

Genotoxicity

Risdiplam was not mutagenic in a bacterial reverse mutation assay. In mammalian cells *in vitro* and in bone marrow of rats, risdiplam increases the frequency of micronucleated cells. Micronucleus induction in bone marrow was observed in several toxicity studies in rats (adult and juvenile animals). The no observed adverse effect level (NOAEL) across the studies was associated with an exposure of approximately 1,5-fold the exposure in humans at the therapeutic dose. Data indicated that this effect is indirect and secondary to an interference of risdiplam with the cell cycle of dividing cells. The same effect is also manifested in other tissues with high cell turnover with changes in the skin, gastrointestinal tract, male germ cells, bone marrow, as well as embryonal toxicity. Risdiplam does not possess a potential to damage DNA directly.

Carcinogenicity

A 2-year carcinogenicity study in rats is ongoing. A carcinogenicity study with risdiplam in rasH2 transgenic mice did not give any evidence for a tumorigenic potential of risdiplam with animals exposed up to 7-fold the exposure in humans at the therapeutic dose.

Reproductive toxicity

In studies in pregnant rats treated with risdiplam, embryofoetal toxicity with reduced foetal weight and delayed development was evident. The NOAEL dose for this effect was approximately two-fold above the exposure levels reached at the therapeutic dose of risdiplam in patients. In studies with pregnant rabbits, embryo-foetal mortality and dysmorphogenic effects were observed at exposures also associated with maternal toxicity. Four foetuses (4%) from 4 litters (22%) developed hydrocephalus. The NOAEL dose for this was approximately four times the exposure levels reached at the therapeutic dose of risdiplam in patients.

In a pre- and post-natal study in rats treated daily with risdiplam, risdiplam caused a slight delay in gestation duration. No adverse effects were recorded on the survival, growth, functional (behavioural or reproductive) performance of the offspring.

Studies in pregnant rats showed that risdiplam crosses the placental barrier and is transferred into the milk.

Other data

Treatment with risdiplam has been associated with cell cycle arrest in male germ cells in rats and monkeys. These effects led to degenerated spermatocytes, degeneration/necrosis of the seminiferous epithelium, and oligo/aspermia in the epididymis. In young rats, effects were seen at exposure levels reached at the therapeutic dose of risdiplam in patients. However, there was no impairment on male fertility seen in a respective study in rats. Sperm cell effects of risdiplam are likely related to an interference of risdiplam with the cell cycle of dividing cells and are stage specific and reversible. No effects were seen on female reproductive organs in rats and monkeys after treatment with risdiplam.

Effect on retinal structure

Chronic treatment of monkeys with risdiplam yielded evidence for an effect on the retina in terms of photoreceptor degeneration starting in the periphery of the retina. Upon cessation of treatment, the effects in the retinogram were partially reversible but the photoreceptor degeneration was not reversible. The effects were monitored by optical coherence tomography (OCT) and by electroretinography (ERG). The effect occurred with an exposure in excess of two times the exposure in humans at the therapeutic dose.

Effect on epithelial tissues

Effects on skin, larynx and eyelid histology and the gastrointestinal tract (GI) tract were evident in rats and monkeys treated with risdiplam. Changes started to be seen with treatment of 2 weeks and longer at more than 2-fold the human exposure). With chronic treatment for 39 weeks in monkeys, the NOAEL was at an exposure of about 2-times the average exposure in humans at the therapeutic dose

Effect on hematological parameters

In the acute bone marrow micronucleus test in rats, a reduction of more than 50% in the ratio of polychromatic (young) to normochromatic (adult) erythrocytes, indicative of substantial bone marrow toxicity, was observed at the high dose level with exposure in excess of 15-times the average exposure in humans at the therapeutic dose. With longer treatment of rats for 26 weeks, the exposure margins to the NOAEL were approximately four times the average exposure in humans at the therapeutic dose.

Juvenile animal studies

Risdiplam was studied for toxicity with chronic administration in rats and monkeys. Studies in juvenile animals showed reduced food intake, slower growth and signs of toxicity in reproductive organs at an exposure to similar to the therapeutic dose for humans.
In terms of toxicity seen after treatment with risdiplam in various organ systems with high cell turnover (skin, GI-tract, bone marrow), animal studies do not indicate any differences in sensitivity between juvenile, adolescent and adult animals.

Other information

Incompatibilities

No incompatibilities between Evrysdi and the recommended reusable syringes for oral administration have been observed.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

The ready-to-use solution is stable for 64 days when stored in the refrigerator (2°C to 8°C).

Special precautions for storage

Powder:
Keep the container in the outer carton in order to protect the contents from light (and moisture).
Do not store above 25°C.

Ready-to-use oral solution:
Keep the container in the outer carton in order to protect the contents from light.
Store in the refrigerator (2-8°C).
Keep the bottle tightly closed and always store in an upright position.

Keep out of the reach of children.

Instructions for handling

- Instructions to observe before, during and after the preparation of the oral solution: The solution must always be prepared by a healthcare professional (e.g. physician or pharmacist).
- Avoid inhaling EVRYSDI powder. Take notice of local regulations and use suitable equipment to prepare the Evrysdi solution.

- Wear gloves.
- Do not use the powder if the expiry date has passed. The expiry date of the powder is printed on the bottle label.
- Do not dispense the reconstituted solution if the “Ready-to-use oral solution. **Expiry date**”- date which is stated on the bottle label and folding box exceeds the original powder expiration date.
- Avoid any contact with the medicine on your skin. If the medicine (powder or solution) gets on your skin, wash the area with water and soap.
- Do not use the medicine if any of the contents of the package are damaged or missing.
- Use purified water or water for injection to prepare the solution.
- Do not add oral syringes other than the ones provided in the carton.
- Do not mix Evrysdi into food or liquids (eg. milk or formula milk).
- Do not mix Evrysdi from the new bottle with the bottle you are currently using.

The patient, respectively, care giver must be instructed by a healthcare professional how the prescribed daily dose is to be prepared and administered before delivery of the prepared solution. (Instructions for use for Evrysdi can be found in the package).

Preparation of the oral solution

Pour 79 ml of purified water or water for injection into the bottle with medication.

Insert the press-in bottle adapter into the opening by pushing it down.

After completely closing the bottle, shake for 15 seconds.

After waiting for 10 minutes, a clear solution should be obtained. If not, shake well again for another 15 seconds.

The “Ready-to-use oral solution. **Do not use after”-date 64 days** after preparation of the solution should be calculated. The day of preparation of the solution is counted as day 0.

The calculated date should be entered on the label of the bottle in the field provided for this purpose under "Ready-to-use oral solution. **Do not use after** (DD.MM.YYYY)" and additionally on the designated field on the outer carton.

For a more detailed description, instructions for preparation for the doctor or pharmacist are included in the package.

Disposal of unused/expired medicines

The release of pharmaceuticals into the environment must be kept as low as possible. Medicines must not be disposed of via wastewater and disposal through household waste should be avoided.

Unused/expired medicines should be disposed of professionally by the dispensing point (doctor or pharmacist).

Marketing authorisation number

67251 (Swissmedic).

Packs

1 bottle containing powder for 80 ml oral solution (0,75 mg/ml risdiplam) [A].
The package also contains one press-in bottle adapter, two reusable 6 ml oral syringes and two reusable 12 ml oral syringes.

Marketing authorisation holder

Roche Pharma (Schweiz) AG, Basel.

Date of revision of the text

April 2021.